Alzheimer's disease. Mutant hippocampal cells having enhanced synaptic potentiation upon tetanic stimulation are contacted with a candidate drug and are subjected to tetanic stimulation. A reduction in synaptic potentiation following contact with the candidate drug is indicative of the efficacy of the candidate drug for treating Alzheimer's disease. Also claimed are mouse cells combined with a candidate drug.

The Pending Claims

Prior to entry of the above amendments Claims 1-12 are pending. Claims 1-9 are directed to a method for screening for drugs for the treatment of Alzheimer's disease. Claims 10-12 are directed mouse hippocampal cells having a mutation in the presenilin gene combined with a candidate drug that inhibits the enhanced synaptic response of the cells to tetani.

The Office Action

Claims 1-12 have been rejected under 35 U.S.C. § 112, first paragraph and Claims 6 and Claims 8-9 have been rejected under 35 U.S.C. § 112,-second paragraph.
Claim 10 has been rejected under 35 U.S.C. § 102(b) as anticipated by Borchelt *et al.*

Amendments

Claim 7 has been cancelled. Claims 1-9 and 10-12 have been amended in order to put the claims in form for allowance or in better form for appeal. The amendments were not made earlier because Applicants believe that the Claims prior to the current amendments were in form for allowance based upon the last office action.

Claims 1-6 have been amended to eliminate the comparison to wild type cells and to instead recite the characteristics of the mutant cells as suggested by the Examiner. Support for the amendments comes from p. 5 line 11, p. 8 line 9, p. 8, line 17 p. 9 line 14 and from p. 9 line 17 of the specification and from the claims as originally filed. Additionally, in Claim 6, the preamble has been amended to reflect the endpoint of the method as stated in the last line of the Claim. Claims 8-9 have been amended to recite the level of significance for the change. Support

for the amendment is found for example on page 6, line 23. Claim 8 also has been amended to recite the characteristics of the mutant cells. Claims 10-12 have been amended to delete "slices of".

Applicants believe that no new matter has been added by any of these amendments and respectfully request the Examiner to enter them.

Response

The Examiner's specific objections and rejections are reiterated below as small indented bold print, followed by applicant's response in normal print.

35 U.S.C. § 112, first paragraph.

Claims 1-12 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record in Paper No. 11, mailed 8-18-99, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicats [*sic*] argue that the phrase which defines the nature of the cells, namely "having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells" is eliminated from consideration. Regardless of the mutation the cells must fulfill the requirement of having enhanced potentiation and so long as it has this effect it is within the scope of the claims. Further, applicant argues that the Parent reference fulfills this requirement of enhanced potentiation and supports the evidence presented in instant application, whether or not there is a difference in the observed fEPSP.

These arguments have been fully considered but are not persuasive as the scope of the claims are not commensurate in scope with enablement. As set forth in Paper No. 11, mailed 8-18-99, Parent et al. teach that no difference was observed between wild-type and mutant hippocampal cells in response to tetanic stimulation which thus represents an example in which applicants method seemingly is contradictory given the Parent cells are also mutant hippocampal cells which do not exhibit enhanced synaptic potentiation. Further, although Parent provides for methods of enhancing long term potentiation in such cells it is clear that this activity is dependent upon many factors which affect synaptic activity including the type of "mutation" the history of synaptic activity, the type of stimulation provided and the measured result, for example fEPSP which is relevant to the determination of synaptic long term potentiation, i.e. a relationship between a presynaptic and postsynaptic nerve. Thus, given the quantity of experimentation necessary for every mutant cell and synaptic history, the impredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim 7 has been cancelled. For the remaining claims, the rejection is believed avoided

by amendment of the claims to delete the comparison to wild type cells and/or to include a description of the characteristics of the mutant cells. The citation of Parent is irrelevant to the claimed invention, which uses as a means of screening for drugs that may be efficacious in treating Alzheimer's disease the ability of those drugs to inhibit the potentiation in mutant cells following tetanic stimulation. It is not important whether the difference in the amount of potentiation between wild type and mutated cells is itself statistically significant, but rather that the difference between mutant cells treated with a candidate drug which is efficacious and those that are untreated is statistically significant. Parent does not mention the effect of such drugs on potentiated mutant cells and therefore is entirely irrelevant. If the cells have an enhanced synaptic potentiation that is comparable to that of hippocampal cells with a PS-1 mutation, the effect can be seen. Applicants have taught throughout the specification how to perform the claimed methods and how to obtain the claimed cells. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. § 112, second paragraph.

> **Claims 6 and 8-9 stand rejected under 35 U.S.C. 112,-second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "statistically significant change" in said claims is still a relative term which renders the claims indefinite because there is no direction as to what level of statistical significance one must achieve. The specification does not provide a standard for ascertaining the requisite degree of change required to exactly constitute a "statistically significant change", and one skilled in the art would not be reasonably apprised of the scope of the invention.**

The rejection of Claims 6 and 8-9 has been avoided by amendment of the claims either to delete the comparison of wild type to mutant cells or to add a level of significance as suggested by the Examiner. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

35 U.S.C. § 102(b)

> **Claim 10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Borchelt et al (October 1997 reference; see PTO-892). Claim 10 is drawn to slices of mouse hippocampal cells having a mutation in a presenilin gene combined with a candidate drug.**

> **Applicants argue that the Examiner has misinterpreted the terms in the claim and that by not]*sic*] stretch of the imagination can one consider an antibody for a neural protein to be a candidate drug.**
>
> **This argument has been fully considered but is not persuasive. There is no reason why an antibody can not be considered a drug since antibodies specifically target and bind to proteins and may be used to block or alter activity. Thus, Borchelt anticipates claim 10.**

The rejection of Claim 10 has been avoided by amendment of the claims to recite that the mouse hippocampal cells are combined with a candidate drug that inhibits the enhanced synaptic response of the cells to tetani. The antibody for the neural protein disclosed by Borchelt et al does not meet these specific limitations and therefore does not anticipate the claimed compositions. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (650) 328-4400.

Respectfully submitted,

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